SYNTHESIS AND METABOLISM OF KETO-HYDROXY ACIDS

BY
WILLIAM CHRISTIAN RISSER
B.S., University of Illinois, 1937

AN ABSTRACT OF A THESIS
SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN
CHEMISTRY IN THE GRADUATE SCHOOL OF
THE UNIVERSITY OF ILLINOIS, 1940

URBANA, ILLINOIS
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PART I

SYNTHESIS AND METABOLISM OF KETO-HYDROXY ACIDS

Introduction

Knoop[1,2] has suggested that the catabolism of α-amino-β-hydroxy acids involves oxidation of the β-hydroxyl group to a β-keto group followed by cleavage of the β-keto acid to glycine and a fatty acid with two less carbon atoms. Knoop excludes the corresponding α-keto-β-hydroxy acid as a possible intermediate on the assumption that such an acid, if formed, would undergo oxidative decarboxylation yielding an α-hydroxy acid with one less carbon atom. This appears to be an unwarranted assumption in view of the possible tautomeric shift of the α-keto-β-hydroxy acid through the ene-diol acid to the corresponding α-hydroxy-β-keto acid. It was the purpose of this investigation, therefore, to develop a method of synthesis of α-keto-β-hydroxy acids and to study their metabolism in order to obtain evidence on this point.

Experimental

Ethyl α, β-ketohydroxy-β-phenylpropionate was prepared by catalytic reduction of ethyl α, β-diketo-β-phenylpropionate. The keto-hydroxy ester reduces Benedict's solution and an acid solution of copper acetate at room temperature. It reacts slowly and incompletely with 2,6-dichlorobenzeneoneindophenol. The keto-hydroxy ester reacts with phenylhydrazine to give 1, 3-diphenyl-4-hydroxy-5-pyrazolone. In pyridine, the keto-hydroxy ester reacts with one mole of benzoyl chloride to produce a single monobenzoate, which was also obtained by the reaction of either ethyl α-keto-β-bromo-β-phenylpropionate or ethyl α-bromo-β-keto-β-phenylpropionate with sodium benzoate. The action of two moles of benzoyl chloride in pyridine converted the keto-hydroxy ester into two dibenzoates of the ene-diol. These are undoubtedly geometric isomers.

The monobenzoate is ethyl α-benzoxy-β keto-β-phenylpropionate as shown by conversion into 1, 3-diphenyl-4-benzoxy-5-pyrazolone with phenylhydrazine.

Summary

Ethyl ∝, β-ketohydroxy-β-phenylpropionate has been prepared by catalytic reduction of ethyl ∝,β-diketo-β-phenylpropionate. Reactions of the keto-hydroxy ester indicate that most of it exists in the ∝-hydroxy-β-keto form.

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PART II

THE METABOLISM OF ∝-AMINO-β-METHOXY-β-PHENYLPROPIONIC ACIDS

Introduction

In connection with studies reported in the previous part, it was decided to investigate the metabolism of ∝-amino-β-methoxy-β-phenylpropionic acids A and B, and of N-benzoyl phenylserine.

Experimental

∝-Amino-β-methoxy-β-phenylpropionic acids A and B were injected intraperitoneally and subcutaneously into dogs and rabbits. In each case the unchanged amino acid was excreted in the urine in high yields.

N-benzoyl phenylserine was excreted in the urine unchanged after intraperitoneal injection into dogs.

It was discovered that rabbits on a diet of milk and eggs excrete considerable amounts of phenaceturic acid in the urine.

Summary

∝-Amino-β-methoxy-β-phenylpropionic acids A and B, and N-benzoyl phenylserine are not altered in passing through the animal body.

Rabbits on a diet of milk and eggs excrete phenaceturic acid in the urine.

PART III

BENZOYL α-AMINOCINNAMIC ACID AZLACTONES

Introduction

Carter[1,2] and co-workers have recently prepared two geometric isomers of benzoyl α-aminocrotonic acid azlactone. In extending this work, a study was made of the azlactonization of N-benzoyl dl-α-amino-β-methoxy-β-phenylpropionic acids A and B.

Experimental

Two geometric isomers of benzoyl α-aminocinnamic acid azlactone were obtained by the action of hot acetic anhydride on either N-benzoyl dl-α-amino-β-methoxy-β-phenylpropionic acid A or B. Azlactone B (m.p. 124°) was readily converted into the stable azlactone A (m.p. 165°) by the action of pyridine or of heat. Each azlactone was hydrolyzed to the corresponding benzoyl α-aminocinnamic acid.

In a study of the properties of the β-phenylethylamine salts of several pairs of N-substituted-dl-α-amino-β-hydroxy (or methoxy) acids, it was discovered that the lower-melting, more soluble disastereoisomer yields the higher-melting, less soluble β-phenylethylamine salt. This has been shown to be true in the following sets of disastereoisomers: Carbobenzoxy dl-α-amino-β-methoxy-β-phenylpropionic acids A and B, benzoyl dl-α-amino-β-methoxy-β-phenylpropionic acids A and B, N-benzoyl dl-threonine and N-benzoyl dl-allothreonine, and in benzoyl O-methyl-dl-threonine and benzoyl O-methyl-dl-allthreonine.

Summary

Two geometric isomers of benzoyl α-aminocinnamic acid azlactone have been prepared and each was hydrolyzed to the corresponding benzoyl α-aminocinnamic acid.

It was discovered that formation of the β-phenylethylamine salts of disastereoisomeric N-substituted dl-α-amino-β-hydroxy (or methoxy) acids causes reversal of melting points and solubilities.

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VITA

The author was born in Washington, Illinois, on May 31, 1915. He was graduated from Washington Community High School in 1933. The following fall he enrolled in Eureka College where he spent three years. His college work was completed at the University of Illinois in 1937, at which time he was granted a B. S. degree. Graduate work at the University of Illinois was pursued the following fall and for the three ensuing years. He was awarded a University Scholarship in his first year, and a University Fellowship the remaining two years of his graduate work.

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